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(54) Title: $\alpha(1,3)$ -GALACTOSYLTRANSFERASE NULL CELLS, METHODS OF SELECTING AND $\alpha(1,3)$ -GALACTOSYLTRANSFERASE NULL SWINE PRODUCED THEREFROM

(57) Abstract: The invention relates to the genetic manipulation of non-human animals. More particularly, the invention relates to genetic manipulation of non-human animals to be used for xenotransplantation. The invention provides a method of selecting GGTA 1 null cells, a viable GGTA 1 null swine, methods for making such swine, and methods of using cells, tissues and organs of such swine for xenotransplantation.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/25199

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A01K 67/027; C12N 5/00, 15/00
US CL : 800/17, 24; 435/325, 375

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 800/17, 24; 435/325, 375

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST, BIOSIS, EMBASE, CAPLUS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NOZAWA, S. et al. Characteristics of Immunoglobulin Gene Usage of the Xenoantibody Binding to Gal-alpha(1,3)Gal Target Antigens in the GAL Knockout Mouse. Transplantation. 15 July 2001, Vol. 72, No. 1, pages 147-155.	1-8, 10-42
A	AYARES, D. et al. Cloning Pigs Deficient in Alpha 1,3 Galactosyltransferase. Graft. January/February 2001, Vol. 4, No. 1, pages 80-82.	1-8, 10-42
A	GOCK, H. et al. Deleting the Gal Epitope from the Donor Pig. Graft. January/February 2001, Volume 4, No. 1, pages 76-77.	1-8, 10-42
A	MIYAGAWA, S. et al. Masking and Reduction of the Galactose-alpha1,3-Galactose (alpha-Gal) Epitope, the Major Xenoantigen in Swine, by the Glycosyltransferase Gene Transfection. Biochemical and Biophysical Research Communications. 1999, Volume 264, pages 611-614.	1-8, 10-42
Y	SAO, H. et al. A New Marrow T Cell Depletion Method Using Anti-CD6 Monoclonal Antibody-Conjugated Magnetic Beads and Its Clinical Application for Prevention of Acute Graft-vs.- Host Disease in Allogeneic Bone Marrow Transplantation: Results of a Phase I-II Trial. International Journal of Hematology. 1999, Volume 69, pages 27-35.	4-8, 10-16



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	POLEJAEVA, I.A. et al. Cloned Pigs Produced by Nuclear Transfer from Adult Somatic Cells. Nature. 07 September 2000, Volume 407, pp. 86-90, especially pages 87-89.	1, 2 and 17-42
Y	ONISHI, A. et al. Pig Cloning by Microinjection of Fetal Fibroblast Nuclei. Science. 18 August 2000, Volume 289, pages 1188-1190, see especially pages 1188 and 1189.	1, 2 and 17-42
Y	BETTHAUSER, J. et al. Production of Cloned Pigs From In Vitro Systems. Nature Biotechnology. October 2000, Volume 18, pages 1055-1059, see especially pages 1055-1058.	1, 2 and 17-42
Y	MCCREATH, K.J. et al. Production of Gene-Targeted Sheep by Nuclear Transfer from Somatic Cells. Nature. 29 July 2000, Volume 405, pages 1066-1069, see especially pages 1067 and 1068.	1, 2 and 17-42
X	WO 95/28412 A1 (BIOTRANSPLANT, INC.) 26 October 1995, see pages 3-14.	1, 2 and 17-33

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/25199

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claim Nos.: 9
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.